Cerebral and splanchnic oxygenation and necrotizing enterocolitis in preterm infants
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ASSESSING CEREBROVASCULAR AUTOREGULATION IN INFANTS WITH NECROTIZING ENTEROCOLITIS USING NEAR-INFRARED SPECTROSCOPY

Trijntje E. Schat, Michelle E. van der Laan, Maarten Schurink, Jan B.F. Hulscher, Christian V. Hulzebos, Arend F. Bos, Elisabeth M.W. Kooi

Pediatric Research, provisionally accepted for publication
ABSTRACT

**Background:** We assessed cerebrovascular autoregulation (CAR) in preterm infants with definite necrotizing enterocolitis (NEC), Bell’s stage 2 or 3, and infants without NEC, using near-infrared spectroscopy (NIRS). We hypothesized that CAR would be more often impaired in infants with NEC compared with infants without NEC.

**Methods:** We measured cerebral regional tissue oxygen saturation, arterial oxygen saturation, and mean arterial blood pressure (MABP) during 48 hours. We calculated the correlation between cerebral fractional tissue oxygen extraction and MABP for each patient. A statistically significant negative correlation reflected impaired CAR.

**Results:** We included fifteen infants with definite NEC (median (range) gestational age (GA) 27.4 (25.6-34.7) weeks, birth weight (BW) 1070 (670-2400) grams) and thirteen infants without NEC (GA 27.9 (26.3-34.7) weeks, BW 980 (640-2640) grams). Fourteen infants had a statistically significant negative correlation (rho -.468 to -.104), of whom five were infants without NEC (5/13; 38%) and nine with definite NEC (9/15; 60%). The difference in prevalence of impaired CAR was not statistically significant.

**Conclusion:** Impaired CAR is present in a substantial proportion of infants with definite NEC, which may predispose them to NEC-associated neurological damage.
INTRODUCTION

Necrotizing enterocolitis (NEC) is a devastating gastrointestinal disease that predominantly affects preterm infants.\(^1\) Several studies demonstrated a strong association between NEC and impaired neurodevelopmental outcome.\(^2-7\) Moreover, neurodevelopmental delay in preterm infants with NEC assessed at school age was found to be associated with more white matter abnormalities as seen on magnetic resonance imaging at term compared to infants who were also born prematurely but who did not have NEC.\(^8\) White matter abnormalities are considered to be the principal anatomic substrate for the neurodevelopmental disability in infants with NEC.\(^9\)

The development of white matter injury depends on the occurrence of two separate mechanisms: infection and/or inflammation and ischemia.\(^10\) Infants with NEC develop an excessive inflammatory response with production of inflammatory toxins.\(^11\) This may affect systemic circulation, and – if severe – also cerebral circulation. Ischemia of cerebral tissue is the result of diminished cerebral blood flow (CBF) caused, amongst others, by impaired cerebrovascular autoregulation (CAR). CAR plays a pivotal role in regulating CBF. When CAR is affected, a pressure-passive cerebral circulation arises, i.e. changes in blood pressure cause changes in CBF. When CBF is low, underperfusion of cerebral tissue ensues, which may lead to cerebral ischemia and subsequent brain damage.

Our research group demonstrated that near-infrared spectroscopy (NIRS) can be used to estimate the presence or absence of CAR in otherwise stable preterm infants, by assessing the relationship between mean arterial blood pressure (MABP) and cerebral fractional tissue oxygen extraction (FTOE). We assumed that a statistically significant negative correlation between MABP and cerebral FTOE reflects impaired CAR. CAR was found to be impaired in 40% of relatively stable preterm infants, also in infants where blood pressures were in the ‘normal’ range.\(^12\) In the absence of CAR, the relationship between MABP and cerebral perfusion is linear. Because FTOE is a reflection of cerebral perfusion, changes in MABP cause opposite changes in cerebral FTOE if CAR is impaired. This linear relationship is independent of the values measured and, as such, can also occur in the presence of blood pressures in the ‘normal’ range.

It is unknown what the prevalence is of impaired CAR in preterm infants with NEC and whether CAR is impaired more often in preterm infants with established NEC than in infants without NEC. Our aim was, therefore, to assess cerebral hemodynamics using NIRS in preterm infants with NEC (Bell’s stage 2 or 3) and without NEC, and to compare the prevalence of impaired CAR between these two groups. We hypothesized that definite NEC would be associated with a higher prevalence of impaired CAR in comparison to infants without NEC, due to the presence of infection/inflammation leading to an affected cerebral circulation.
METHODS

Study population

We included infants with definite NEC who were part of a larger, prospective observational cohort study performed in the neonatal intensive care unit of University Medical Center Groningen, between October 2010 and October 2012. This study was registered in the Dutch Trial Registry under number NTR3239. Infants who were suspected of NEC or who had been diagnosed with NEC were included. Suspected NEC was defined as the presence of non-specific abdominal symptoms. NEC was diagnosed when pneumatosis intestinalis, portal venous gas, or both were present on abdominal radiographic examination. After completion of the study, an expert panel of consultant neonatologists and pediatric surgeons independently classified the infants into the modified Bell’s stages. Consensus was reached in all cases. For the purpose of this study, we included only those preterm infants with a continuous invasive arterial blood pressure measurement who were diagnosed with definite NEC. We defined the onset of NEC symptoms as the time of the first abdominal radiographic examination taken after clinical suspicion of NEC, including those taken in referring hospitals. The study was approved by the institutional ethics review board of University Medical Center Groningen. Written parental informed consent was obtained in all cases.

We selected control infants that were admitted to our neonatal intensive care unit between October 2010 and December 2012. The attending neonatologist decided on NIRS monitoring on clinical grounds. We only included infants with a gestational age (GA) < 35 weeks, with an indwelling arterial catheter for constant blood pressure measurements. Exclusion criteria were the presence of NEC or sepsis.

Near-infrared spectroscopy

We measured cerebral regional tissue oxygen saturation ($r_{SO_2}$) continuously with a near-infrared spectrometer (INVOS 5100C, Covidien, Mansfield, MA, USA). The neonatal Somasensor (Covidien) was placed on the frontoparietal side of the infant’s head and was secured with elastic bandaging or Mepitel (Mölnlycke, Sweden).

The sensor emits two wavelengths (730 and 810 nm) in the cerebral tissue. The two receivers, at 30 and 40 mm distance from the emitter, receive the reflected light as a function of wavelength. Hence, the spectral absorption of the underlying tissue can be determined. Since oxygenated and deoxygenated hemoglobin each absorb and reflect near-infrared light at the two wavelengths differently, it is possible to calculate regional tissue oxygen saturation, i.e. microvascular oxygenation.

We measured arterial oxygen saturation (SpO$_2$) (Nellcor, Covidien) simultaneously with $r_{SO_2}$ and calculated cerebral FTOE using the formula: FTOE = SpO$_2$ - $r_{SO_2}$ / SpO$_2$. FTOE reflects the balance between tissue oxygen supply and tissue oxygen consumption. As cerebral oxygen consumption is thought to be relatively stable in preterm infants, FTOE can be used as an indicator of tissue perfusion.

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**Analysis of cerebrovascular autoregulation**

A blood pressure dependent CBF (pressure-passive CBF) can be the result of two mechanisms: blood pressures below the autoregulatory threshold or impaired CAR. Cerebral FTOE was found to be inversely related to CBF.

In the presence of impaired CAR, FTOE will also be blood pressure dependent. In that case, low blood pressures cause higher cerebral oxygen extraction in order to meet the needs for normal cerebral metabolism. We used this negative relationship between arterial blood pressure and cerebral FTOE to assess the absence of CAR. We considered a statistically significant negative correlation coefficient as indicating impaired CAR.

**Clinical data**

We collected the following neonatal demographic and clinical characteristics: birth weight (BW), GA, postnatal age at first NIRS measurement, the concentration of hemoglobin (Hb), glucose, carbon dioxide (pCO₂), and C-reactive protein (CRP), the need of mechanical ventilation, and mortality. Additionally, we documented the administration of red blood cell transfusions, volume expansion, and inotropes, and the presence of a hemodynamically significant PDA during the study period. Hemodynamically significant patent ductus arteriosus (PDA) was defined as a diastolic forward flow in the branches of the pulmonary artery, a diastolic backflow in the descending aorta, and a left ventricular end diastolic diameter > the 95th centile.

We determined Hb and pCO₂ as the first value just before or during the NIRS recording period. The glucose concentration is based on the lowest value during NIRS recording, while the CRP concentration is based on the highest value during NIRS recording.

**Statistics**

In infants with NEC, r₂SO₂ recording started as soon as possible after clinical signs and symptoms suggested the presence of NEC. We sampled one random value of r₂SO₂, SpO₂, FTOE, and MABP every 5 minutes for 48 consecutive hours for both infants with NEC and control infants. Next, we calculated 48-hour mean values for each variable. Artifacts in the measurements were not taken into the analyses. The Spearman rank test was used to calculate the correlation coefficients between MABP and cerebral FTOE, sampled every 5 minutes, for each preterm infant individually. Next, we compared the prevalence of impaired CAR between infants without NEC and infants with definite NEC (Bell’s stage 2 or 3) using Fisher exact test.

We compared proportions of categorical data with Fisher exact test and median values were analyzed by using the Mann-Whitney test for non-normal distributions. We used SPSS 22.0 software for Windows (IBM SPSS Statistics 22, IBM Corp., Armonk, New York, USA) for all our statistical analyses. A P value of < .05 was considered statistically significant.
RESULTS

We included fifteen infants with definite NEC and thirteen control patients. We present the patient characteristics for the two groups in Table 1. Infants with NEC had significantly higher pCO$_2$ and CRP concentrations. NIRS monitoring in infants with NEC had started significantly later compared with the control group. Furthermore, infants with definite NEC received inotropes, volume expansion, and RBC transfusions significantly more often during the study period compared with controls.

Of the six infants with NEC who died, four infants did so as a result of circulatory and respiratory insufficiency within the 48-hour study period. The fifth infant died due to circulatory insufficiency ten days after the NIRS measurements - most likely as a result of an anastomotic leak. The sixth infant died 89 days after the study period due to irreversible brain damage, which most likely occurred during surgery for an intestinal obstruction. The infant without NEC who died, did so 66 days after the study period, due to bronchopulmonary dysplasia.

In the infants with NEC, NIRS recordings started after a median time of 11 hours (range, 2-29) after onset of NEC symptoms and were discontinued preliminary in six infants due to the presence of pneumoperitoneum on abdominal radiographic examination.

Out of the fifteen infants in the NEC group, we found nine (60%) with a statistically significant negative correlation between MABP and cerebral FTOE. Out of the thirteen infants without NEC, we found five infants (38%) with a statistically significant negative correlation. This difference was not statistically significant ($P = .449$). Table 2 shows the correlation coefficients with associated $P$ values per infant.

In Figure 1 we present the correlation coefficients between cerebral FTOE and MABP for one infant with NEC with a statistically significant negative correlation suggesting impaired CAR and for one infant without NEC without a statistically significant negative correlation suggesting adequate CAR. The infant with definite NEC was monitored for 8 hours until pneumoperitoneum was detected on abdominal radiographic examination. The infant was taken to theatre shortly afterwards.

DISCUSSION

We demonstrated that 60% of preterm infants with definitive NEC (Bell's stage 2 and 3) had a statistically significant negative correlation between cerebral FTOE and MABP, suggesting impaired CAR. This is a high percentage in comparison to the preterm infants without NEC (38%). Nevertheless, this difference was not statistically significant.

For preterm infants who suffered NEC, the short-term and long-term neurological sequelae can be devastating. Timely identification of infants with impaired CAR is, therefore, important in order to prevent the development of white matter abnormalities. Our data indicate that, to this end, NIRS is a useful, non-invasive, bedside monitoring method.

Several studies investigated the presence of CAR in preterm infants using near-infrared spectroscopy.$^{12,18-22}$ The prevalence of pressure-passivity ranged from 14 to 53%. These
Assessing cerebrovascular autoregulation in infants with necrotizing enterocolitis using near-infrared spectroscopy

Table 1. Patient characteristics of infants without NEC and infants with definite NEC.

<table>
<thead>
<tr>
<th></th>
<th>No NEC (n = 13)</th>
<th>Definite NEC (n = 15)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gestational age (weeks)</td>
<td>27.9 (26.3-34.7)</td>
<td>27.4 (25.6-34.7)</td>
</tr>
<tr>
<td>Birth weight (grams)</td>
<td>980 (640-2640)</td>
<td>1070 (670-2400)</td>
</tr>
<tr>
<td>Postnatal age (days)</td>
<td>4 (3-13)</td>
<td>10 (3-34)</td>
</tr>
<tr>
<td>Male/Female</td>
<td>6/7</td>
<td>10/5</td>
</tr>
<tr>
<td>Bell’s stage 2/Bell’s stage 3</td>
<td>N/A</td>
<td>5/10</td>
</tr>
<tr>
<td>Hemoglobin (mmol/L)</td>
<td>8.3 (7.3-10.5) (n = 10)</td>
<td>7.4 (6.0-12.0)</td>
</tr>
<tr>
<td>pCO₂ (kPa)</td>
<td>5.6 (4.8-6.6) (n = 10)</td>
<td>6.5 (4.4-10.1)</td>
</tr>
<tr>
<td>Glucose (mmol/L)</td>
<td>4 (3.2-7) (n = 7)</td>
<td>6.5 (3.2-8.6)</td>
</tr>
<tr>
<td>CRP (mg/L)</td>
<td>0 (0-8) (n = 7)</td>
<td>110 (7-425)**</td>
</tr>
<tr>
<td>Mechanical ventilation (%)</td>
<td>6 (46)</td>
<td>12 (80)</td>
</tr>
<tr>
<td>hsPDA (%)</td>
<td>4 (31)</td>
<td>1 (7)</td>
</tr>
<tr>
<td>Inotropes (%)</td>
<td>0 (-)</td>
<td>7 (47)*</td>
</tr>
<tr>
<td>Volume expansion (%)</td>
<td>1 (8)</td>
<td>12 (80)**</td>
</tr>
<tr>
<td>RBC transfusion (%)</td>
<td>1 (8)</td>
<td>8 (53)*</td>
</tr>
<tr>
<td>Mortality (%)</td>
<td>1 (8)</td>
<td>6 (40)</td>
</tr>
</tbody>
</table>

Data are expressed as median (range) or as numbers unless specified otherwise.

Abbreviations: hsPDA - hemodynamically significant patent ductus arteriosus; N/A - not applicable; RBC - red blood cell.

Statistical differences between the two groups are marked by * (< .05) or ** (< .001).

studies, however, all used different parameters to assess CAR and also performed their analyses differently, a fact which complicates any comparison. Our definition of impaired CAR was based on a study performed previously in our research group. Verhagen et al. demonstrated that 40% of clinically stable preterm infants had a statistically significant negative correlation between cerebral FTOE and MABP. We found similar results in our control group.

In preterm infants with definite NEC, we found a statistically significant negative correlation, which suggested impaired CAR, between cerebral FTOE and MABP in 60% of cases. A possible explanation for this higher percentage could be that preterm infants with NEC might have had blood pressures under the lower limit of the autoregulatory curve, with a consequential pressure-passive CBF. We did not find statistically significant negative correlations between cerebral FTOE and MABP for those infants who had the lowest mean MABP. Indeed, it was suggested that impaired CAR might develop when blood pressures are in the range of what we now define as ‘normal’ and ‘safe’. In these instances, it is of the utmost importance to only allow minimal decreases in blood pressure in order to prevent low cerebral perfusion and the subsequent risk of developing brain injury.

Factors that were found to be associated with impaired CAR are low BW, low GA, low Hb, low glucose, and high pCO₂ concentrations. PCO₂ concentrations were significantly higher in preterm infants with NEC, which suggests a possible contributing role of pCO₂ in causing pressure-passive CBF in the preterm infants with NEC we studied. Nevertheless, we would like to stress that in our study group the pCO₂ values were based on single
measuring cerebrovascular autoregulation in infants with necrotizing enterocolitis using near-infrared spectroscopy

Additionally, infants with NEC received inotropes more often compared with infants without NEC. It was found that treated hypotension was associated with short- and long-time morbidity, which suggests an indirect relationship between inotropes and a pressure passive cerebral circulation.\textsuperscript{27,28} Furthermore, a direct negative influence of dopamine on CAR has been reported.\textsuperscript{29} Conversely, several studies demonstrated a protective role of inotropes by means of increasing CBF.\textsuperscript{30-32}

Limitations of this study are the small size of the sample and the variation in the duration of the r\textsubscript{c}SO\textsubscript{2} measurements for assessing CAR. These varied between 2 and 47 hours. Recent

Table 2. Individual correlation coefficients between cerebral FTOE and MABP, sampled every five minutes.

<table>
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<tr>
<th>Infant</th>
<th>Bell's stage</th>
<th>Measurement time in hours</th>
<th>MABP</th>
<th>FTOE</th>
<th>Spearman's rho</th>
<th>P value</th>
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</table>

The mean values of MAPB en FTOE are presented. Correlation coefficients are based on the correlation between MABP and FTOE, sampled every 5 minutes.

\textsuperscript{†}indicates infant who died.
research suggested that pressure-passivity can be transiently impaired. In infants whom we measured for a short period of time we might, on the one hand, have measured an episode in which pressure-passivity was present or, on the other hand, an episode in which this was not the case. It is, therefore, possible that in such instances we either underestimated or overestimated the prevalence of impaired CAR. Furthermore, Verhagen et al. reported some limitations of the technique and of the method of analysis we used to assess CAR. Even so, our data, as well as those of the study performed by Verhagen et al., demonstrated that a considerable proportion of preterm infants can be identified as having impaired CAR by using the correlation between 5-minute measurements of cerebral FTOE and MABP.

In conclusion, we demonstrated that 60% of preterm infants with NEC had a statistically significant negative correlation between cerebral FTOE and MABP, which may be indicative of impaired CAR. Our findings may imply that a pressure-passive CBF can be the underlying pathophysiological substrate for the development of white matter abnormalities and the long-term neurodevelopmental impairments in a substantial proportion of preterm infants with NEC. Furthermore, our results indicated that in those infants in whom NIRS measurements suggested impaired CAR, fluctuations in blood pressure could be potentially harmful. This warrants monitoring blood pressure closely as well as monitoring cerebral oxygenation by means of NIRS. Future studies need to be performed to elucidate when and how we need to intervene.

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REFERENCES


